date of the shipment by the manufacturer and shall include the name and address of the consignee, the date and quantity shipped, and the manufacturing dates, control numbers, or marks identifying the Type A medicated article(s) shipped.

§226.115 Complaint files.

Records shall be maintained for a period of 2 years of all written or verbal complaints concerning the safety or efficacy of each Type A medicated article(s). Complaints shall be evaluated by competent and responsible personnel and, where indicated, appropriate action shall be taken. The record shall indicate the evaluation and the action.

PART 250—SPECIAL REQUIREMENTS FOR SPECIFIC HUMAN DRUGS

Subpart A—Drugs Regarded as Misbranded

Sec.

250.10 Oral prenatal drugs containing fluorides intended for human use.

250.11 Thyroid-containing drug preparations intended for treatment of obesity in humans.

250.12 Stramonium preparations labeled with directions for use in self-medication regarded as misbranded.

Subpart B—New Drug or Prescription Status of Specific Drugs

250.100 Amyl nitrite inhalant as a prescription drug for human use.

250.101 Amphetamine and methamphetamine inhalers regarded as prescription drugs.

250.102 Drug preparations intended for human use containing certain "coronary vasodilators."

250.103 Thorium dioxide for drug use.

250.104 [Reserved]

 ${\small 250.105~Gelsemium-containing~preparations} \\ {\footnotesize regarded~as~prescription~drugs}.$

250.106 Cobalt preparations intended for use by man.

250.107 [Reserved]

250.108 Potassium permanganate preparations as prescription drugs.

Subpart C—Requirements for Drugs and Foods

250.201 Preparations for the treatment of pernicious anemia.

Subpart D—Requirements for Drugs and Cosmetics

250.250 Hexachlorophene, as a component of drug and cosmetic products.

AUTHORITY: Secs. 201, 306, 402, 502, 503, 505, 601(a), 602 (a) and (c), 701, 705(b) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 336, 342, 352, 353, 355, 361(a), 362 (a) and (c), 371, 375(b))

SOURCE: 40 FR 14033, Mar. 27, 1975, unless otherwise noted.

Subpart A—Drugs Regarded as Misbranded

§250.10 Oral prenatal drugs containing fluorides intended for human

(a) The Food and Drug Administration finds that there is neither substantial evidence of effectiveness nor a general recognition by qualified experts that prenatal drug preparations containing fluorides promote tooth development in the fetus, prevent dental caries in the offspring, or prevent dental caries in pregnant women.

(b) Any such drug preparation that is so labeled, represented, or advertised will be regarded as misbranded and subject to regulatory proceedings unless such recommendations are covered by a new-drug application, including substantial evidence of effectiveness, approved pursuant to section 505 of the Federal Food, Drug, and Cosmetic Act. Any such drug preparation that is labeled, represented, or advertised as containing fluorides as an active ingredient of the drug for prenatal use will similarly be regarded as misbranded and subject to regulatory proceedings.

(c) A completed and signed "Investigational New Drug Application," set forth in part 312 of this chapter, must be submitted to cover clinical investigations designed to obtain evidence that such preparations are effective for such use.

(d) Regulatory proceedings may be initiated with respect to drug preparations shipped within the jurisdiction of the act that are contrary to provisions of this statement after 30 days from the date of publication of this statement in the FEDERAL REGISTER.

 $[40\ FR\ 14033,\ Mar.\ 27,\ 1975,\ as\ amended\ at\ 55\ FR\ 11577,\ Mar.\ 29,\ 1990]$

EFFECTIVE DATE NOTE: At 62 FR 12084, Mar. 14, 1997, §250.10 was removed, effective Apr. 14, 1997.

§ 250.11 Thyroid-containing drug preparations intended for treatment of obesity in humans.

(a) Investigation by the Food and Drug Administration has revealed that a large number of drug preparations containing thyroid or thyrogenic substances in combination with central nervous system stimulants, with or without one or more additional drug substances such as barbiturates or laxatives, are being marketed for or as adjuncts to the treatment, control, or management of obesity in humans. The Commissioner of Food and Drugs finds that the administration of such combinations for said purposes is without medical rationale except possibly in those relatively uncommon instances where the condition is directly related to hypothyroidism and there exists a concurrent need for appetite control (in such instances the safety and effectiveness of such combinations are not generally recognized). In particular, the Commissioner of Food and Drugs finds that neither the consensus of informed medical opinion nor clinical experience justifies any representation that such combinations are safe and effective in connection with the treatment, control, or management of obesity in patients having normal thyroid function.

(b) Combinations of thyroid or other thyrogenic drugs with central nervous system stimulants with or without other drug substances when offered for or as adjuncts to the treatment, control, or management of obesity not related to hypothyroidism are regarded as misbranded. Such combinations when offered for obesity in humans directly attributable to established hypothyroidism are regarded as new drugs within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act.

§ 250.12 Stramonium preparations labeled with directions for use in self-medication regarded as misbranded.

(a) Stramonium products for inhalation have been offered for use in the therapy of the acute attacks of bronchial asthma for many years although their reliability and effectiveness are questionable. Recently, a significantly increased number of reports have come to the attention of the Food and Drug Administration showing that such products have been subject to abuse and misuse on a fairly large scale, mostly by young people, through oral ingestion for the purpose of producing hallucinations. Reports of such use have been received from physicians and police and other law enforcement authorities. Reports have also appeared in the public press and in medical jour-

- (b) Labeling these products with a warning that they are not for oral ingestion has not been effective in protecting the public. Misuse of stramonium preparations can cause serious toxic effects including toxic delirium, visual disturbances, fever, and coma. A number of serious reactions have already occurred from the oral ingestion of such products.
- (c) On the basis of this information, the Commissioner of Food and Drugs has concluded that such articles have a potentiality for harmful effect through misuse and are not safe for use except under the supervision of a physician. In the interest of public health protection, therefore, the Food and Drug Administration adopts the following policy:
- (1) Preparations containing stramonium supplied from the leaves, seeds, or any other part of the plant in the form of a powder, pipe mixture, cigarette, or any other form, with or without admixture of other ingredients, will be regarded as misbranded if they are labeled with directions for use in self-medication.
- (2) The Food and Drug Administration will, on request, furnish comment on proposed labeling limiting any such preparation to prescription sale.
- (d) The labeling or dispensing of stramonium preparations contrary to this statement after 60 days following the date of its publication in the FEDERAL REGISTER may be made the subject of regulatory proceedings.

Subpart B—New Drug or Prescription Status of Specific Drugs

§250.100 Amyl nitrite inhalant as a prescription drug for human use.

(a) Amyl nitrite inhalant has been available over-the-counter for emergency use by the patient in the management of angina pectoris for a number of years. As a result of a proposed policy statement published August 25, 1967 (32 FR 12404), the Commissioner of Food and Drugs received reports of the abuse of this drug by those who do not require it for medical purposes. Additionally, comment included a great deal of concern expressed by individual physicians, medical associations, pharmaceutical associations, manufacturers, and State and local health authorities. Based on the information available, it is the opinion of the Commissioner of Food and Drugs, concurred in by the Food and Drug Administration Medical Advisory Board, that amyl nitrite inhalant is a drug with a potentiality for harmful effect and that it should be removed from over-thecounter status and restricted to sale on the prescription of a practitioner licensed by law to administer such drug.

(b) Therefore, amyl nitrite inhalant will be regarded as misbranded unless the labeling on or within the package from which the drug is to be dispensed bears adequate information for its safe and effective use by physicians, in accordance with §201.100(c) of this chapter, and its label bears the legend "Caution: Federal law prohibits dispensing without prescription."

(c) Regulatory proceedings may be initiated with regard to the interstate shipment of amyl nitrite inhalant that is labeled, advertised, or dispensed contrary to this statement of policy if such act occurs after July 1, 1969.

§ 250.101 Amphetamine and methamphetamine inhalers regarded as prescription drugs.

(a) Recurring reports of abuse and misuse of methamphetamine (also known as desoxyephedrine) inhalers show that they have a potentiality for harmful effect and that they should not be freely available to the public through over-the-counter sale. From complaints by law-enforcement offi-

cials, health officials, individual physicians, parents, and others as well as from Food and Drug Administration investigations, it is evident that the wicks from these inhalers are being removed and the methamphetamine they contain is being used as a substitute for amphetamine tablets. Amphetamine tablets and amphetamine inhalers have been restricted to prescription sale because of their potentiality for harm to the user.

(b) It is the considered opinion of the Food and Drug Administration that, in order to adequately protect the public health, inhalers containing methamphetamine or methamphetamine salts (d-desoxyephedrine, or dl-desoxyephedrine, or their salts), as well as amphetamine inhalers should be restricted to prescription sale and should be labeled with the legend "Caution: Federal law prohibits dispensing without prescription."

§250.102 Drug preparations intended for human use containing certain "coronary vasodilators."

(a) (1) The Food and Drug Administration finds that the following "coronary vasodilators" are extensively regarded by physicians as safe and useful as employed under medical supervision for the management of angina pectoris in some patients:

Amyl nitrite. Erythrityl tetranitrate. Mannitol hexanitrate. Nitroglycerin. Potassium nitrite. Sodium nitrite.

Inositol hexanitrate.

(2) Additionally, new-drug applications have been approved for products containing:

Isosorbide dinitrate.
Octyl nitrite.
Pentaerythritol tetranitrate.
Triethanolamine trinitrate biphosphate (trolnitrate phosphate).

(b) The Food and Drug Administration also finds that there is neither substantial evidence of effectiveness nor a general recognition by qualified experts that such drugs are effective for any of the other purposes for which some such drugs are promoted to the

medical profession in labeling and advertising. In particular, neither clinical investigations nor clinical experience justify any representations that such drugs are effective in the management of hypertension; in the management of coronary insufficiency or coronary artery disease, except for their anginal manifestations; or in the management of the post coronary state, except angina pectoris present after coronary occlusion and myocardial infarction.

- (c) Any preparation containing such drugs that is labeled or advertised for any use other than management of angina pectoris, or that is represented to be efficacious for any other purpose by reason of its containing such drug, will be regarded by the Food and Drug Administration as misbranded and subject to regulatory proceedings, unless such recommendations are covered by the approval of a new-drug application based on a showing of safety and effectiveness.
- (d) Any such drug in long-acting dosage form is regarded as a new drug that requires an approved new-drug application before marketing.
- (e) Any of the drugs listed in paragraph (a) (2) of this section is regarded as a new drug that requires an approved new-drug application. Articles for which new-drug approvals are now in effect should be covered by supplemental new-drug applications as necessary to provide for labeling revisions consistent with this policy statement.

§ 250.103 Thorium dioxide for drug use.

(a) Thorium dioxide is a source of naturally occurring radioactivity that has been used over a period of years as a radiopaque medium. When thorium dioxide is injected, it is permanently stored in the body. Because of its radioactivity, this storage causes scarring and carcinogenesis in the area of storage. There are reports in the medical literature of malignancy and deaths resulting from the injection of thorium dioxide. Therefore, the use in man of drugs containing thorium dioxide is justified only when this drug has a unique clinical usefulness and there is substantial evidence of limited life expectancy by reason of disease or advanced age. The administration of the drug to food-producing animals cannot be justified since it may result in residues of the drug in food.

- (b) Drugs containing thorium dioxide are unsafe and are regarded as misbranded within the meaning of section 502(f) (1), (2), and (j) of the Federal Food, Drug, and Cosmetic Act when labeled or advertised for administration to man except when they have a unique clinical usefulness and there is substantial evidence of limited life expectancy by reason of disease or advanced age.
- (c) Drug preparations containing thorium dioxide may be approved for marketing on the basis of new-drug applications containing labeling bearing, in addition to other requirements, information to the following effect, which differs substantially from the labeling that has been employed in the past in the marketing of such drugs:
- (1) Warning. For use only when this drug has a unique clinical usefulness and there is substantial evidence of limited life expectancy by reason of disease or advanced age. Not for administration to food-producing animals.
- (2) *Precautions.* Special precautions should be taken to prevent soft tissue extravasation of the injected material. Precautions should be taken to prevent injection of thorium dioxide into the subarachnoid space.
- (3) *Indications for use.* For demonstration of primary or secondary tumors in the liver; for the delineation of the wall of a cystic malignant brain tumor when such delineation is deemed advantageous for purposes of progressive monitoring in the course of therapy.
- (4) *Dosage.* Minimum amount necessary for adequate visualization should be utilized.
- (d) A new drug application will be regarded as approvable if it contains appropriate labeling conforming to the provisions of paragraph (c) of this section and satisfactory information of the kinds required by §314.50 of this chapter.

[40 FR 14033, Mar. 27, 1975, as amended at 55 FR 11577, Mar. 29, 1990]

EFFECTIVE DATE NOTE: At 62 FR 12084, Mar. 14, 1997, §250.103 was removed, effective Apr. 14, 1997.

§250.104 [Reserved]

§ 250.105 Gelsemium-containing preparations regarded as prescription drugs.

It is the consensus of informed medical opinion that the margin of safety between the therapeutic and toxic concentration of gelsemium is narrow and it is difficult to predict the point at which the dose will be toxic. Very small doses may cause toxic symptoms. It is therefore the view of the Food and Drug Administration that gelsemium is not a proper ingredient in any product that is to be sold without prescription. Accordingly, any drug containing gelsemium will be regarded as misbranded under section 503(b)(4) of the Federal Food, Drug, and Cosmetic Act if its label fails to bear in a prominent and conspicuous fashion the statement 'Caution: Federal law prohibits dispensing without prescription.'

§ 250.106 Cobalt preparations intended for use by man.

- (a) On January 17, 1967 (21 CFR 3.48; 32 FR 449), the Commissioner of Food and Drugs issued a revised statement of policy with respect to the status of cobalt-containing drug preparations intended for use by man, which revision was to be modified as needed following consideration of such drugs by a panel of hematologists. A panel consisting of authorities in the field of hematology met on March 8, 1967, with representatives of the Medical Advisory Board for the Food and Drug Administration to consider the status of cobalt-containing drugs and the following findings and recommendations were made:
- (1) Cobalt salts are not suitable for over-the-counter sale to the public for the treatment of iron-deficiency anemia. They are associated with toxic effects and offer no advantage over iron alone.
- (2) Potential toxic effects of these salts includes liver damage, claudication, myocardial damage, thyroid hyperplasia, hypothyroidism, dermatitis, nausea, and anorexia.
- (3) Cobalt salts are not generally recognized as safe or effective therapy for any disease condition.
- (b) On the basis of the available evidence and the findings and rec-

- ommendations of the representatives of the Medical Advisory Board, the Commissioner of Food and Drugs finds and determines with respect to cobalt-containing drug preparations intended for use by man, except radioactive forms of cobalt and its salts and cobalamin and its derivatives, that:
- (1) Such articles, because of their potential for causing toxic effects, are not suitable for over-the-counter use in iron-deficiency anemia; any such article that is labeled, represented, or advertised for over-the-counter use in the prevention or treatment of iron-deficiency anemia will be regarded as subject to regulatory proceedings.
- (2) Such articles are not generally recognized by qualified experts as safe or effective therapeutic agents for iron-deficiency anemia or for any condition whether for over-the-counter sale or for prescription dispensing; any such article labeled, represented, or advertised for any condition will be regarded as subject to regulatory proceedings unless such recommendations are covered by a new-drug application approved pursuant to section 505 of the Federal Food, Drug, and Cosmetic Act and based on a showing of safety and effectiveness.
- (3) Cobalt salts added to drugs in small amounts are not effective for any purpose and should be removed.
- (c) A completed and signed "Investigational New Drug Application," set forth in part 312 of this chapter, must be submitted to cover clinical investigations to obtain evidence that such preparations are safe and effective for any purpose.
- (d)(1) For such preparations for which new-drug approvals are in effect, supplemental new-drug applications may be submitted if changes consistent with this policy statement can be effected thereby. If the composition and labeling of an article are such that the cobalt is not significant in relation to the labeling claims, it will be permissible for the applicant to remove the cobalt salt from the formulation, delete all references to it in the labeling and resume marketing the reformulated drug, provided that a supplement is submitted within 30 days from the

date of publication of this policy statement in the FEDERAL REGISTER furnishing full information regarding such changes, including the date on which such changes are being effected.

(2) Applicants holding other approved new-drug applications for such preparations should submit, within 30 days, a written statement waiving opportunity for a hearing preliminary to withdrawing approval of the application unless the applicant wishes to avail himself of the opportunity for a hearing.

(e) Regulatory proceedings may be initiated with respect to any drug within the jurisdiction of the act that is contrary to the provisions of:

- (1) Paragraph (b) of this section and shipped after the date of publication of this policy statement in the FEDERAL REGISTER.
- (2) Paragraphs (c) and (d) of this section and shipped after 30 days from the date of publication of this policy statement in the FEDERAL REGISTER.

 $[40\ FR\ 14033,\ Mar.\ 27,\ 1975,\ as\ amended\ at\ 55\ FR\ 11577,\ Mar.\ 29,\ 1990]$

EFFECTIVE DATE NOTE: At 62 FR 12084, Mar. 14, 1997, §250.106 was removed, effective Apr. 14, 1997.

§250.107 [Reserved]

§ 250.108 Potassium permanganate preparations as prescription drugs.

(a) There have been a number of reports in the medical literature of serious injuries to women resulting from the misuse of potassium permanganate in an effort to induce abortion. Reports from physicians who have treated such cases show that the injuries are commonly caused by introducing tablets or crystals of potassium permanganate into the vagina. Experience with these cases shows that such use of potassium permanganate is not effective in producing abortion, but that instead the drug produces serious and painful injury to the walls of the vagina, causing ulcers, massive hemorrhage, and infection. Such dangerous and useless employment of potassium permanganate is apparently encouraged among the misinformed by the mistaken idea that the vaginal bleeding caused by the corrosive action of the drug indicates a termination of pregnancy, which it does not.

(b) Potassium permanganate is a strong oxidizing agent, a highly caustic, tissue-destroying chemical, and a poison. There are no circumstances under which crystals and tablets of potassium permanganate constitute safe dosage forms for use in self-medication. It is the consensus of informed medical opinion that the only dosage forms of potassium permanganate known to be safe for use in self-medication are aqueous solutions containing not more than 0.04 percent potassium permanganate. Such solutions are safe for use in self-medication only by external application to the skin.

(c) In view of the very real potentiality for harmful effect, and the actual injuries caused by the misuse of potassium permanganate, the Food and Drug Administration believes that in order adequately to protect the public health:

(1) Potassium permanganate and potassium permanganate tablets intended for human use are drugs subject to section 503(b)(1) of the Federal Food, Drug, and Cosmetic Act and should be restricted to prescription sale. Such drugs will be regarded as misbranded if at any time prior to dispensing the label fails to bear the legend, "Caution: Federal law prohibits dispensing without prescription."

(2) Potassium permanganate labeled for use as a prescription component in human drugs under the exemption provided in §201.120 of this chapter or labeled for manufacturing use under the exemption provided in §201.122 of this chapter will be regarded as misbranded unless the label bears the statement, "Caution: Federal law prohibits dispensing without prescription."

(3) These drugs will be regarded as misbranded when intended for veterinary use unless the label bears the legend, "Caution: Federal law restricts this drug to sale by or on the order of a licensed veterinarian"; *Provided, however,* That this shall not apply to a drug labeled and marketed for veterinary use if such drug contains not more than 50 percent of potassium permanganate and includes other ingredients which make it unsuitable for human use and unlikely that the article would be used in an attempt to induce abortion.

- (4) Any preparation of potassium permanganate intended for over-the-counter sale for human use internally or by application to any mucous membranes or for use in the vagina will be regarded as misbranded under the provisions of section 502(f) (1) and (2) and section 502(j) of the act.
- (5) Any other preparation of potassium permanganate intended for overthe-counter sale for human use will be regarded as misbranded under section 502(f) (1) and (2) and section 502(j) of the act unless, among other things, all of the following conditions are met:
- (i) It is an aqueous solution containing not more than 0.04 percent potassium permanganate.
- (ii) The label and labeling bear, in juxtaposition with adequate directions for use, clear warning statements designated as "Warning," and to the effect: "Warning—For external use on the skin only. Severe injury may result from use internally or as a douche. Avoid contact with mucous membranes."
- (d) The labeling or dispensing of any potassium permanganate preparations intended for drug use within the jurisdiction of the Federal Food, Drug, and Cosmetic Act contrary to this statement after 60 days from the date of its publication in the FEDERAL REGISTER may be made the subject of regulatory proceedings.

Subpart C—Requirements for Drugs and Foods

§250.201 Preparations for the treatment of pernicious anemia.

- (a) The ninth announcement of the Anti-anemia Preparations Advisory Board of the United States Pharmacopeia is concerned with the status of the treatment of pernicious anemia. It clearly presents the following facts:
- (1) The Sixteenth Revision of the Pharmacopeia of the United States, which became official on October 1, 1960, does not include preparations intended for the treatment of pernicious anemia by oral administration.
- (2) The U.S.P. unit for anti-anemia preparations no longer has any significance.
- (3) The U.S.P. Anti-anemia Preparations Advisory Board was disbanded.

- (b) On the basis of the scientific evidence and conclusions summarized in the statement of the U.S.P. Anti-anemia Preparations Advisory Board as well as pertinent information from other sources, the Commissioner of Food and Drugs finds it is the consensus of well informed medical opinion that:
- (1) The parenteral administration of cyanocobalamin or vitamin B_{12} is generally recognized as a fully effective treatment of pernicious anemia. Parenteral cyanocobalamin preparations have not been and are not authorized for use except by or on the prescription of a duly licensed medical practitioner.
- (2) Some patients afflicted with pernicious anemia do not respond to orally ingested products. There is no known way to predict which patients will fail to respond or will cease to respond to the treatment of pernicious anemia with orally ingested preparations.
- (3) The substitution of a possibly inadequate treatment, such as the ingestion of oral preparations of vitamin B_{12} with intrinsic factor concentrate, in place of parenteral vitamin B_{12} products for a disease condition as serious as pernicious anemia cannot be regarded as safe in all cases.
- (4) The development of the classical symptoms of pernicious anemia that would cause a person to seek medical attention may in some cases be delayed by oral ingestion of intrinsic factor. Pernicious anemia is a disease that is associated, among other things, with a higher than normal incidence of cancer of the stomach and that for the safety of the patient, requires continuous expert medical supervision.
- (5) With inadequate treatment there may be markedly deleterious effects on the nervous system. It is well established that whereas the development of anemia is completely reversible with adequate treatment, the involvement of the nervous system may not be completely reversible and thus may result in permanent damage.
- (6) Some hematologists prescribe oral preparations of vitamin B_{12} in the treatment of pernicious-anemia patients.
- (7) Intrinsic factor and intrinsic factor concentrate serve no known useful

therapeutic or nutritive purpose except to the extent that they do increase the gastrointestinal absorption of vitamin B_{12} in patients with a deficiency or absence of intrinsic factor, which may eventually lead to pernicious anemia. This conclusion does not apply to diagnostic procedures using radioactive cyanocobalamin.

(8) Medical expertise is required for the diagnosis as well as the manage-

ment of pernicious anemia.

(c) The Eleventh Edition of The National Formulary and its first Interim Revision include monographs for oral preparations of vitamin B_{12} with intrinsic factor concentrate, establish a unit of vitamin B_{12} with intrinsic factor concentrate, and provide for a National Formulary Anti-anemia Preparations Advisory Board to assign the potency of such preparations. This provides for the availability of such oral preparations, standardized within the meaning of the broad limits characteristic of the evaluation of such preparations.

(d) Any drug that is offered for or purports to contain intrinsic factor or intrinsic factor concentrate will be regarded as misbranded within the meaning of section 503(b) of the Federal Food, Drug, and Cosmetic Act unless it is labeled with the legend "Caution—Federal law prohibits dispensing with-

out prescription."

(e) Any drug for oral ingestion intended, represented, or advertised for the prevention or treatment of pernicious anemia or which purports to contain any substance or mixture of substances described in paragraph (d) of this section (other than diagnostic radioactive drugs containing cyanocobalamin) will be regarded as misbranded under sections 502(f)(2) and (j) of the act unless its labeling bears a statement to the effect that some patients afflicted with pernicious anemia may not respond to the orally ingested product and that there is no known way to predict which patients will respond or which patients may cease to respond to the orally ingested products. The labeling shall also bear a statement that periodic examinations and laboratory studies of pernicious anemia patients are essential and recommended.

(f) Under section 409 of the Federal Food, Drug, and Cosmetic Act, intrinsic factor and intrinsic factor concentrate are regarded as food additives. No food additive regulation nor existing extension of the effective date of section 409 of the act authorizes these additives in foods, including foods for special dietary uses. Any food containing added intrinsic factor or intrinsic factor concentrate will be regarded as adulterated within the meaning of section 402(a)(2)(C) of the act.

(g) Regulatory action may be initiated with respect to any article shipped within the jurisdiction of the act contrary to the provisions of this policy statement after the 180th day following publication of this statement in the FEDERAL REGISTER.

Subpart D—Requirements for Drugs and Cosmetics

§ 250.250 Hexachlorophene, as a component of drug and cosmetic products

(a) Antibacterial component. The use of hexachlorophene as an antibacterial component in drug and cosmetic products has expanded widely in recent years. It is used in such products because of its bacteriostatic action against gram-positive organisms, especially against strains of staphylococcus; however, hexachlorophene offers no protection against gram-negative infections. In addition the anti-bacterial activity depends largely on repeated use. A notice published in the FEDERAL REGISTER of April 4, 1972 (37 FR 6775), invited data on OTC antimicrobial ingredients, including hexachlorophene, for review by an OTC Drug Advisory Review Panel to be convened under the procedures set forth in the FEDERAL REGISTER of May 11, 1972 (37 FR 9464). This statement of policy will remain in effect unless and until replaced by a monograph resulting from the OTC Drug Advisory Review

(b) Adverse effects. Though considered safe for many years, recent information has become available associating hexachlorophene with toxic effects, including deaths. Studies have shown that toxic amounts of hexachlorophene

can be absorbed through the skin of humans, especially the skin of premature babies or damaged skin. Human toxicity reports include data on symptomatology, blood and tissue levels of hexachlorophene, and descriptions of neuropathologic lesions. Recent infant deaths due to use of baby powder accidentally contaminated with 6 percent hexachlorophene have occurred. The accumulated evidence of toxicity is sufficient to require that continued marketing of hexachlorophene containing products be carefully defined in order to protect consumers.

- (c) Prescription drugs. (1) Because of their potential for harmful effect, containing hexachlorophene, other than as a preservative as described below, are not considered to have been shown to be safe and effective, are regarded as new drugs requiring approved new drug applications, and would be misbranded for over-thecounter distribution. In the interest of health protection, hexachlorophene containing drugs will be regarded as misbranded and subject to regulatory proceedings unless the label bears the legend "Caution: Federal law prohibits dispensing without a prescription," and the labeling on or within the package from which the drug is to be dispensed bears adequate information for its safe and effective use by practitioners, in accord with §201.100(c) of this chapter.
- (2) The Food and Drug Administration recognizes that hexachlorophene is useful as a bacteriostatic skin cleanser. It further concludes that the margin of safety is such that products containing hexachlorophene may appropriately be used within clearly delineated conditions of use.
- (3) In order for such drugs to bear adequate information for safe and effective use the following statements are representative of the type of labeling for products shown to be effective bacteriostatic skin cleansers. Labeling for products other than bacteriostatic skin cleansers will be determined through the new drug procedures based on the available data.
- (i) In the labeling other than on the immediate container label.

INDICATIONS

- 1. Bacteriostatic skin cleanser for surgical scrubbing or handwashing as part of patient care.
- 2. For topical application to control an outbreak of gram-positive infection where other infection control procedures have been unsuccessful. Use only as long as necessary for infection control.

CONTRAINDICATIONS

- 1. Not for use on burned or denuded skin or on mucous membranes. $\,$
- 2. Not for routine prophylactic total body bathing.

WARNINGS

Rinse thoroughly after use. Patients should be closely monitored and use should be immediately discontinued at the first sign of any of the symptoms described below.

Hexachlorophene is rapidly absorbed and may produce toxic blood levels when applied to skin lesions such as ichthyosis congenita or the dermatitis of Letterer-Siwe's syndrome or other generalized dermatologic conditions. Application to burns has also produced neurotoxicity and death.

Infants have developed dermatitis, irritability, generalized clonic muscular contractions and decerebrate rigidity following application of a 6 percent hexachlorophene powder. Examination of brainstems of those infants revealed vacuolization like that which can be produced in newborn experimental animals following repeated topical application of 3 percent hexachlorophene. Moreover, a study of histologic sections of premature infants who died of unrelated causes has shown a positive correlation between hexachlorophene baths and lesions in white matter of brains.

(ii) On the immediate container label prominently displayed and in bold print:

"Special Warning: This compound may be toxic if used other than as directed. Rinse thoroughly after use. Monitor patients closely for toxicity symptoms."

(4) Marketing of products for the indications listed in paragraph (c)(3) of this section may be continued without an approved new drug application (or required supplement thereto) either until a notice of opportunity for hearing is issued on a proposal by the Director of the Center for Drug Evaluation and Research to refuse to approve such new drug application (or required supplement) or until January 31, 1978,

whichever comes first, if all the following conditions were met after September 27, 1972:

- (i) The product is labeled with the prescription legend and adequate information for safe and effective use as set forth in paragraph (c)(3) of this section.
- (ii) Within 30 days, or by (10-27-72) the holder of an approved new drug application submits a supplement to provide for the revised label and full disclosure labeling. As the label and labeling will have been put into use, the supplement should be submitted under the provision of §314.70(c)(2) of this chapter.

(iii) Within 30 days, or by (10-27-72) the holder of an approved new drug application submits a supplement to provide for a revised formulation where appropriate to comply with this order.

(iv) Within 90 days, or by (12–26–72) the holder of an approved new drug application submits a supplement containing blood level data obtained from use of the drug as recommended, unless such information is a part of the new drug application file.

(v) Within 90 days, or by (12–26–72), the manufacturer or distributor of such a drug for which a new drug approval is not in effect submits a new drug application in accord with §314.50 of the new drug regulations (21 CFR 314.50), including blood level data obtained from use of the drug as recommended.

- (5) Prescription drug products may contain hexachlorophene as part of an effective preservative system only under the conditions and limitations provided for under paragraph (d) of this section.
- Over-the-counter (OTC) drugs. Over-the-counter drug products, other than those which in normal use may be applied to mucous membranes or which are intended to be used on mucous membranes, may hexachlorophene only as part of an effective preservative system, at a level that is no higher than necessary to achieve the intended preservative function, and in no event higher than 0.1 percent. Such use of hexachlorophene shall be limited to situations where an alternative preservative has not yet been shown to be as effective or where adequate integrity and stability data for the reformulated product are not

yet available. This use of hexachlorophene will not, by itself, require an approved new drug application. Use of hexachlorophene as a preservative at a level higher than 0.1 percent is regarded as a new drug use requiring an approved new drug application, which must be submitted within the time set out in paragraph (c) (4) of this section.

- (e) Cosmetics. Hexachlorophene may be used as a preservative in cosmetic products other than those which in normal use may be applied to mucous membranes or which are intended to be used on mucous membranes, at a level that is no higher than necessary to achieve the intended preservative function, and in no event higher than 0.1 percent. Such use of hexachlorophene shall be limited to situations where an alternative preservative has not yet been shown to be as effective or where adequate integrity and stability data for the reformulated product are not yet available. The component of a preservative system whether hexachlorophene antimicrobial agent, should be selected on the basis of the effect on the total microbial ecology of the product, not merely on gram-positive bacteria.
- (1) Adequate safety data do not presently exist to justify wider use of hexachlorophene in cosmetics.
- (2) Antibacterial ingredients used as substitutes for hexachlorophene in cosmetic products, and finished cosmetic products containing such ingredients, shall be adequately tested for safety prior to marketing. Any such ingredient or product whose safety is not adequately substantiated prior to marketing may be adulterated and will in any event be deemed misbranded unless it contains a conspicuous front panel statement that the product has not been adequately tested for safety and may be hazardous.
- (f) Content statement. All reference to hexachlorophene limit in this order is on a weight-in-weight (w/w) basis. Quantitative declaration of hexachlorophene content on the labeling of the products, where required, shall be on a w/w basis.
- (g) Shipments of products. Shipments of products falling within the scope of paragraphs (c), (d), or (e) of this section

which are not in compliance with the guidelines stated herein shall be the subject of regulatory proceedings after the effective date of the final order.

- (h) *Prior notices.* This order preempts any conditions for marketing products set forth in the following prior notices.
- 1. DESI No. 4749 (34 FR 15389, October 2, 1969), ''Certain OTC Drugs for Topical Use.''
- 2. DESI No. 2855 (35 FR 12423, August 4, 1970), "Certain Mouthwash and Gargle Preparations."
- 3. DESI No. 8940 (36 FR 14510, August 6, 1971), "Topical Cream Containing Pyrilamine Maleate, Benzocaine, Hexachlorophene, and Cetrimonium Bromide."
- 4. DESI No. 6615 (36 FR 18022, September 8, 1971), "Deodorant/Antiperspirant."
 5. DESI No. 6270 (36 FR 23330, December 8,
- 5. DESI No. 6270 (36 FR 23330, December 8, 1971), "Certain Preparations Containing Hexachlorophene".

[40 FR 14033, Mar. 27, 1975, as amended at 42 FR 63773, Dec. 20, 1977; 55 FR 11577, Mar. 29, 1990]

PART 290—CONTROLLED DRUGS

Subpart A—General Provisions

Sec.

290.5 Drugs; statement of required warning.290.6 Spanish-language version of required warning.

290.10 Definition of emergency situation.

Subpart B [Reserved]

Subpart C—Requirements for Specific Controlled Drugs [Reserved]

AUTHORITY: Secs. 502, 503, 505, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 352, 353, 355, 371).

Source: 40 FR 14040, Mar. 27, 1975, unless otherwise noted.

Subpart A—General Provisions

§290.5 Drugs; statement of required warning.

The label of any drug listed as a "controlled substance" in schedule II, III, or IV of the Federal Controlled Substances Act shall, when dispensed to or for a patient, contain the following warning: "Caution: Federal law prohibits the transfer of this drug to any person other than the patient for whom it was prescribed." This statement is not required to appear on the label of a controlled substance dis-

pensed for use in clinical investigations which are "blind."

$\S\,290.6$ Spanish-language version of required warning.

By direction of section 305(c) of the Federal Controlled Substances Act, \$290.5, promulgated under section 503(b) of the Federal Food, Drug, and Cosmetic Act, requires the following warning on the label of certain drugs when dispensed to or for a patient: "Caution: Federal law prohibits the transfer of this drug to any person other than the patient for whom it was prescribed." The Spanish version of this is: "Precaucion: La ley Federal prohibe el transferir de esta droga a otra persona que no sea el paciente para quien fue recetada."

§ 290.10 Definition of emergency situation.

For the purposes of authorizing an oral prescription of a controlled substance listed in schedule II of the Federal Controlled Substances Act, the term *emergency situation* means those situations in which the prescribing practitioner determines:

- (a) That immediate administration of the controlled substance is necessary, for proper treatment of the intended ultimate user; and
- (b) That no appropriate alternative treatment is available, including administration of a drug which is not a controlled substance under schedule II of the Act, and
- (c) That it is not reasonably possible for the prescribing practitioner to provide a written prescription to be presented to the person dispensing the substance, prior to the dispensing.

Subpart B [Reserved]

Subpart C—Requirements for Specific Controlled Drugs [Reserved]

PART 291—DRUGS USED FOR TREATMENT OF NARCOTIC ADDICTS

Sec.

291.501 Narcotic drugs in the maintenance treatment of narcotic addicts.